Naloxone modulates visual judgments of similarity but not dissimilarity

Krummenacher, P ; Kut, E ; Folkers, G ; Brugger, P

Abstract: Endogenous opioids have been implicated in mediating (placebo) analgesia, in reward processes, and in the regulation of socially relevant emotions. To explore their potential contributions to higher cognitive functions, we used a novel task with tachistoscopically presented (for 150 ms) pairs of meaningless figures. Healthy right-handed men judged the similarities and dissimilarities between the two figures on a visual analogue scale (VAS) in two separate runs. In a double-blind, between-subjects design, subjects were administered intravenously either 0.2-mg/kg naloxone or placebo 10 min prior to the task, and VAS judgments and response latencies were measured. We found a significant interaction between substance group and type of judgment: The magnitude of the similarity judgments was lower in the naloxone than in the placebo group, while dissimilarity judgments remained uninfluenced by the treatment. Reaction latencies and mood scores, assessed before and after substance administration, did not differ between the two groups, indicating that the findings did not rely on altered motor performance or motivation. We suggest that naloxone decreased the "similarity criterion" in comparative judgments, indicating its potentially modulatory effect on visual cognition. The task introduced here could be used for the implicit study and quantification of subtle affective-cognitive processes beyond the level of mere questionnaire data.

DOI: https://doi.org/10.3758/s13415-013-0155-9

Naloxone modulates visual judgments of similarity but not dissimilarity

Peter Krummenacher*[1,2,3]; Elvan Kut[2]; Gerd Folkers[2]; Peter Brugger[1]

[1]Department of Neurology, Neuropsychology Unit, University Hospital Zurich, Switzerland

[2]Collegium Helveticum, Schmelzbergstrasse 25, CH- 8092 Zurich, Switzerland

[3]Department of Psychology, Clinical Psychology and Psychotherapy, University of Basel, Switzerland

*Correspondence should be addressed to Dr. Peter Krummenacher, Department of Psychology, Clinical Psychology and Psychotherapy, University of Basel, Missionsstrasse 62, CH-4055 Basel, Switzerland,
E-mail address: peter.krummenacher@unibas.ch
Tel.: +41(0) 61 26 70212; fax: +41(0) 61 26 70339

Running title: naloxone and cognitive relatedness

Total number of words: 2636

Abstract

Endogenous opioids have been implicated in mediating (placebo) analgesia, in reward processes and in the regulation of socially relevant emotions. To explore their potential contribution to higher cognitive functions, we used a novel task with tachistoscopically (150ms) presented pairs of meaningless figures. Healthy right-handed men judged the similarities and dissimilarities between the two figures on a visual analogue scale (VAS) in two separate runs. In a double-blind, between-subject design, participants were administered either 0.2 mg/kg naloxone intravenously or placebo 10 minutes prior to the task. VAS judgments and response latencies were measured. There was a significant interaction between substance group and type of judgment; the magnitude of similarity judgments was lower in the naloxone than in the placebo group, while dissimilarity judgments remained uninfluenced by the treatment. Reaction latencies and mood scores, assessed before and after substance administration, did not differ between the two groups, indicating that the findings do not rely on altered motor performance or motivation. We infer that naloxone decreased the “similarity criterion” in comparative judgments, indicating its modulatory effect on visual cognition. The task introduced here could be used for the implicit study and quantification of subtle affective-cognitive processes beyond the level of mere questionnaire data.

Keywords: Naloxone, Similarity, Dissimilarity, visual Judgments, Cognition

Introduction

Endogenous opioid systems have mainly been implicated in affective processes such as the response to reward (Smith and Berridge, 2007), the modulation of endocrine functions (e.g. Drolet et al., 2001), the regulation of affect (e.g. Zubieta et al., 2003), pleasure-related analgesia (Leknes and Tracey, 2008, Kut et al., 2011) and the mediation of (placebo) analgesia (e.g. Petrovic et al., 2002). Moreover, several lines of evidence indicate that the neurocircuitry and neurochemistry of physical pain overlap with those of more abstract, complex cognitive-affective experiences such as social emotions (Macdonald and Leary, 2005, Stein et al., 2007), in particular social attachment (Herman and Panksepp, 1978, Panksepp et al., 1980, Moles et al., 2004, Barr et al., 2008). In a recent neuroimaging study with healthy subjects, Eisenberger et al. (2003) showed that neural networks activated during distress caused by social exclusion are also activated during physical pain and that pain experience can be reduced by visual stimuli signalling attachment (Eisenberger et al., 2011). In line with these findings of “social distance regulation” is the general explanation for the feeling of physical pain that accompanies emotional loss (Panksepp, 2003), whether it be the loss of a loved one (Zubieta et al., 2003), rejection by one's social group (Eisenberger et al., 2003, Eisenberger et al., 2006), or the distress experienced by young animals when being separated from their parents (Panksepp, 1998).

In healthy humans, opioid agonists have been implicated in feelings of emotional relatedness or social emotions and in mood-elevating effects (Schaffer et al., 2007, Gospic et al., 2008, Koepp et al., 2009). By contrast, the mu-opioid antagonist naloxone has been shown to influence endocrine functions (Drolet et al., 2001) and occasionally reported to induce dysphoric mood states at doses over 0.25 mg/kg (Mendelson et al., 1978, Grevert et al., 1983, Martin del Campo et al., 1992, Martin del Campo et al., 1994). However, it remains

to be established in how far discrepancies in study findings may be a consequence of the lack of a reliable measure and methodological difficulties.

Most surprisingly, beside reported opioidergically modulated mood effects, only a few studies have so far investigated influences on other higher brain functions such as naloxone-dependent alterations in attention (Buchsbaum et al., 1982, Arnsten et al., 1983, Arnsten et al., 1984) and memory (Cohen et al., 1983, Kamboj et al., 2005, Friswell et al., 2008). More recently, Biederman and colleagues suggested that mu-opioids are involved in perceptual pleasure (Biederman and Vessel, 2006, Yue et al., 2007). However, their influence on cognitive judgmental processes is largely unexplored. Endogenous opioids' influence on cognitive functioning is thus of central importance for both, basic and clinical research (Ersek et al., 2004 for a clinical review).

From a phenomenological perspective, a cognitive equivalent to emotional feelings of relatedness, or more broadly "social emotions", could be conceptualized as "coherence perception" or distance regulation. Judgments of similarity/dissimilarity are an important, often neglected, component in a variety of cognitive processes, including object recognition (Barenholtz and Tarr, 2008), semantic and perceptual categorization (Pettigrew, 1958), esthetics (Wertheimer, 1923/1958), and analogic reasoning (Novick, 1988) and belief formation (Gianotti et al., 2001). Spotting similarity has also been proposed to be a fundamental aspect of various cognitive processes such as making inferences, knowledge generalization, and knowledge transfer (e.g. Gentner et al., 1993).

Although the question of how people judge similarity and dissimilarity is clearly of critical importance in social cognition (e.g. Mitchell et al., 2006) and in cognitive psychology, little is known about its neurochemical underpinnings and whether it can be considered a

distinct cognitive system. We here introduce a novel judgment task assessing “cognitive relatedness” or formal visual coherence/contrast perception. In a visual perceptual task stimulating cognitive judgments of visual similarity and dissimilarity we investigated whether a mu-opioid receptor antagonist (naloxone) could modify healthy subjects’ judgments of similarity/dissimilarity. We predicted decreased similarity (coherence perception) and increased dissimilarity (contrast perception) judgments in participants receiving a naloxone injection. Moreover, we hypothesized a dissociation of similarity and dissimilarity, i.e. we assumed that they would not represent two endpoints on a bipolar scale, but instead provide two independent, context-related frames of reference.

Material and Methods

Subjects:

Volunteers were 21 advertisement-recruited healthy right-handed men (mean handedness score (Chapman and Chapman, 1987) = 13.9, SD = 1.6, range = 13 – 19), 19 – 44 years of age (mean = 26.7, SD = 7.4). All subjects gave written informed consent to the experimental procedures, which had been approved by the local ethics committee.

Health status of the participants was assessed with a detailed questionnaire (Campbell, 2000). All subjects confirmed the absence of any relevant acute or chronic disease (hypertension, heart disease, renal disease, liver disease, mental illness, or seizure disorder), a history of neurological disorder, a mental illness or mental impairment. Participants also denied having a history of abuse of medications, drugs or alcohol and any recreational consumption of drugs, narcotics or other CNS-relevant substances over the last three months. Participation in the study paid 50 Swiss francs.

Participants were tested individually. They were seated on a comfortable reclining chair in front of a 15.2 – inch (diagonal) computer screen. Room lighting and screen contrast were all kept constant.

Presentation of all instructions was carried out via computer display and automatically controlled by “Superlab Pro 4” (Cedrus©) running on an Apple G4 Powerbook©,™. Distance between head and computer screen was adjusted to permit undisturbed view and was kept at approximately 60 cm for all participants.

Questionnaire

Measurement of participants’ mood: Participants rated their mood two times, once at the beginning and once at the end of the experiment. Ratings were assessed with 24 adjectives

from the German mood questionnaire Multidimensional Mood questionnaire (MDBF) (1997)). The MDBF questionnaire is a short, multidimensional, self-evaluative questionnaire that describes the current mood state of an individual on three dimensions “good vs. bad mood,” “wakefulness vs. sleepiness,” and “calmness vs. restlessness.”

Judgment tasks

Similarity and dissimilarity judgment tasks. Eighteen different stimulus pairs consisting of two horizontally placed meaningless geometric figures were tachistoscopically presented (exposure time = 150 ms). One figure of a pair was presented to the left, and the other to the right side of a central fixation cross (horizontal eccentricity = 1.5° to 3.0° of visual angle). The single pairs were constructed respecting the Gestalt laws of proximity, good continuation, closure, similarity, and figure/ground properties. Each stimulus pair was also presented in a vertically mirrored version. There were two counterbalanced runs consisting of 36 trials; in one subjects had to indicate similarity (SJ: similarity judgment) and in the other dissimilarity (DJ: dissimilarity judgment) with a computer mouse in their right hand on a 9-inch bipolar visual analogue scale (VAS) presented against a light gray background (Figure 1). All objects (object size: within 2.8 x 2.8 cm, lines thickness: 2 point) were printed in black and presented on a computer screen (gray background). Sample stimuli are illustrated in Fig.1. Stimulus pairs were identical in both the SJ and DJ runs, but presented in a different, pseudorandomized order.

Participants were asked to rest their head on a chin rest, and to fixate the cross in the centre of the screen during stimulus exposure. They were instructed to respond as quickly and intuitively as possible and were told that their preference ratings on similarity/dissimilarity judgments were highly subjective and that there were neither false nor correct judgments.

---------- INSERT FIGURE 1 ABOUT HERE ----------

Double–blind procedure

Naloxone administration. The study had a randomized, double-blind, placebo-controlled, between-subject design. Naloxone hydrochloride (n = 10, 0.2 mg / kg bodyweight, concentration 1mg/ml, pharmacy of the Kanton Zürich) or the equivalent volume of NaCl (n = 9, 0.9 %, pharmacy of the Kanton Zürich), respectively was administered. Similar naloxone dosages have been previously shown to completely antagonize endogenous opioid-mediated analgesia in healthy volunteers (Amanzio and Benedetti, 1999). To prevent high stress levels during the experiment, a nurse laid an intravenous catheter at the inner elbow of the non-dominant arm 10 minutes prior to task administration. The entire testing was supervised by a medical doctor. All participants had been asked to refrain from any alcohol, caffeine- or taurin-containing beverage for at least 12 hours before the start of the experiment and confirmed their compliance in the debriefing. At the end of behavioral testing, participants were asked (by questionnaire) which substance they thought they had received.

Data analysis

Two separate two-way ANOVAs with substance group (naloxone vs. placebo) as between-subject factors, and run (similarity vs. dissimilarity rating) as repeated measures were calculated for the position on the VAS (VAS-magnitude in percent) and reaction latencies. Homogeneity of variances was checked using Levene's test ($F = 1.775$, $p = .149$); and normal distribution of the dependent variables was tested by the Kolmogorov-Smirnov test ($Z \leq .732$, $p \geq .657$). If not otherwise stated, tests are two-tailed with an alpha-level at 0.05.

Outlier detection was performed by the Grubb-Test. To test for a naloxone influence on psychometrically assessed mood, a three-way repeated measure ANOVA was computed comprising the between-subject factor substance (naloxone vs. placebo), and the within-subject factors time (beginning vs. end of the experiment) and mood dimension (valence, wakefulness, calmness).

Two subjects did not adhere to the judgment task instruction and constantly pressed the keyboard instead of using the mouse to indicate the degree of similarity or dissimilarity on the VAS. Valid data were thus available from 19 participants.

Results

Handedness, Age and Blinding

Participants in the naloxone and placebo group did not differ from one another in age ($t(17) = -1.72$, $p = .11$) and the strength of right-handedness ($t(17) = 1.78$, $p = .112$).

There was no association between what substance participants believed they had received (drug or placebo) and what they had actually received, which suggests that blinding was effective ($\chi 2 = 0.259$ $p = .611$): eighty-four percent of the study participants believed they had received saline. Two participants who thought they had received naloxone were in the placebo group and one participant under the influence of naloxone correctly detected the substance.

Questionnaires

Mood ratings (MDBF) assessed at the beginning and the end of the experiment did not differ significantly from each other nor were there any interactions with substance type (all F-values ≤ 2.241, corresponding p-values ≥ .122).

Cognitive Judgment Tasks

No significant main effects were found for VAS magnitudes (all F-values ≤ 1.684, corresponding p-values ≥ .212). However, the two-way ANOVA for the VAS magnitude revealed a significant interaction between *substance group* and *run* ($F(1,17) = 10.460$, $p = .005$; see Figure 2).

Post hoc comparisons for this interaction showed a higher VAS magnitude in the placebo (mean = 57.09, SD = 6.30) than in the naloxone group (mean = 68.25, SD = 12.56) for similarity judgments ($p = .023$) but a comparable VAS magnitude between the naloxone (60.54, SD = 8.31) and placebo group (60.17, SD = 14.30) for dissimilarity judgments ($p = .945$). Moreover, while in the placebo group VAS magnitudes were higher for similarity than for dissimilarity judgments ($p = .036$), VAS magnitudes for similarity and dissimilarity in the naloxone group were not significant different from one another ($p = .085$).

----------INSERT FIGURE 2 ABOUT HERE----------

Reaction latencies: there were no significant main effects or interactions (all F-values ≤ 1.716, corresponding p-values ≥ .208).

Discussion

Healthy participants were administered a novel perceptual cognitive judgment task assessing visual similarity and dissimilarity. In a double-blind, naloxone, placebo-controlled between-subject design we aimed to investigate a role of endogenous opioids in “cognitive relatedness”.

We focused on the hypothesis that a cognitive equivalent to social distance regulation might be conceptualized as “cognitive relatedness”, and could be dependent on mu-opioid receptor activity.

In short, the results both support and contradict our original hypothesis. The kind of coherence perception interacted with naloxone administration. More specifically, the VAS magnitude of similarity judgments but not dissimilarity judgments of visual presented object pairs were more moderate (e.g. a shift towards low similarity) for participants in the naloxone than in the placebo group. Reaction latencies did not differ in the two groups. In addition, psychometrically assessed mood did not differ between the placebo and naloxone group. Therefore, the effects of altered VAS magnitudes are unlikely to simply reflect naloxone-induced altered motor performance and/or motivation and thus did not confound the operationalization of the cognitive judgments.

High similarity was perceived differently from low dissimilarity but only in the placebo, but not in the naloxone group. The VAS magnitude of similarity was more pronounced than that of dissimilarity.

We thus infer that the opioid antagonist naloxone decreased the “analogy criterion” in visual cognitive-affective judgments, but only when framed for similarity, but not for dissimilarity. This finding demonstrates a modulatory effect of naloxone on judgments of cognitive relatedness and suggests that some aspects of formal cognition, i.e. the readiness

to judge something as similar and simultaneously as dissimilar might be dependent on mu-opioid receptor activity.

Clearly, although we did not find psychometrically assessed mood differences between the placebo and naloxone group, further research needs to disentangle whether the altered cognitive strategies in similarity judgments are due to naloxone-induced changes in the affective system (i.e. a mildly detached or dysphoric mood) or are the result of a specific, opioid-associated cognitive focusing on formal stimulus properties perceived to be related to one another. This could be done through use of more elaborated and combined formally complex and affectively loaded visual stimuli and by showing an accentuation of similarity judgments under the influence of opioidergic agonists. Most insightful would be a replication of our approach using positron-emission tomography with [(11)C]carfentanil (Zubieta et al., 2003) to measure possible cortical regional mu-opioid receptor availability in vivo. Indeed, a high density of mu-opioid receptors in the brains of macaque monkeys (Lewis et al., 1981, Wise and Herkenham, 1982) and similar findings in human subjects (Quirion and Pilapil, 1991), has been found to be distributed along a gradient that increases in density along the ventral visual pathway and in association areas such as the parahippocampal cortex.

One may dare to surmise that distinct biological systems are specifically involved in the neuronal generation of coherence perception. This type of perception, if not a human equivalent of “social emotions” in animals (Herman and Panksepp, 1978, Panksepp et al., 1980, Panksepp, 2003), may arguably be at the heart of spotting similarities in objects, minds and intentions that surround an individual. Under this broad perspective, one further effect uncovered in the present study deserves to be mentioned. Judging two stimuli as highly similar in the similarity judgment run was no indicator of how dissimilar those same stimuli would be perceived in the dissimilarity judgment run. That is, the perception of relatedness, or “coherence perception”, is by no means a homogenous perceptual-cognitive

act. Rather, emphasis on resemblance and unity may principally differ from a focus on distinctive features of scene or social interaction.

From a methodological point of view, classical self-report measures for affective states have cast doubt on the reliability of these measurements (e.g. Clark and Schober, 1992, Tourangeau et al., 2000). Our novel task could thus provide a non-verbal, indirect, sensitive cognitive measure for the implicit study and quantification of subtle affective-cognitive (51)[51][51][51] processes such as pain judgment and evaluative reasoning beyond the level of mere questionnaire data. To conclude, whether the glass is judged half-full or half-empty may (see Figure 3 for an illustrative ambigram) depend on the rater's balancing of positive and negative affect. The former tends to promote cognitive, "relational processes", whereas the latter may inhibit relational processing and narrow down the focus on stimulus-specific processing (Clore and Palmer, 2008).

----------INSERT FIGURE 3 ABOUT HERE----------

Disclosure/Conflict of interest

The authors declare that they have no competing financial interests.

Acknowledgements

Inspired by and dedicated to late Jugg U. Storck. We thank Dana Briegel and Jan von Overbeck for their medical support and Marianne Regard for helpful comments on this manuscript. This research was supported by the Cogito Foundation.

References

Amanzio M, Benedetti F (1999) Neuropharmacological dissection of placebo analgesia: expectation-activated opioid systems versus conditioning-activated specific subsystems. J Neurosci 19:484-494.

Arnsten AF, Neville HJ, Hillyard SA, Janowsky DS, Segal DS (1984) Naloxone increases electrophysiological measures of selective information processing in humans. J Neurosci 4:2912-2919.

Arnsten AF, Segal DS, Neville HJ, Hillyard SA, Janowsky DS, Judd LL, Bloom FE (1983) Naloxone augments electrophysiological signs of selective attention in man. Nature 304:725-727.

Barenholtz E, Tarr MJ (2008) Visual judgment of similarity across shape transformations: evidence for a compositional model of articulated objects. Acta Psychol (Amst) 128:331-338.

Barr CS, Schwandt ML, Lindell SG, Higley JD, Maestripieri D, Goldman D, Suomi SJ, Heilig M (2008) Variation at the mu-opioid receptor gene (OPRM1) influences attachment behavior in infant primates. Proceedings of the National Academy of Sciences of the United States of America 105:5277-5281.

Biederman I, Vessel E, A. (2006) Perceptual Pleasure and the Brain. American Scientist 94:247-253.

Buchsbaum MS, Reus VI, Davis GC, Holcomb HH, Cappelletti J, Silberman E (1982) Role of opioid peptides in disorders of attention in psychopathology. Ann N Y Acad Sci 398:352-365.

Campbell JJ (2000) Neuropsychiatric assessment. In: Textbook of Geriatric Neuropsychiatry(Coffey, C. and Cummings, E., eds), pp 109-124 Washington, DC: American Psychiatric Press.

Chapman LJ, Chapman JP (1987) The measurement of handedness. Brain and Cognition 6:175-183.

Clark HH, Schober MF (1992) Asking questions and influencing answers. In: Questions About Questions(Tanur, J. M., ed), pp 15-48 New York: Russel Sage.

Clore GL, Huntsinger JR (2007) How emotions inform judgment and regulate thought. Trends Cogn Sci 11:393-399.

Clore GL, Palmer J (2008) Affective guidance of intelligent agents: How emotion controls cognition. Cognitive Systems Research.

Cohen RM, Cohen MR, Weingartner H, Pickar D, Murphy DL (1983) High-dose naloxone affects task performance in normal subjects. Psychiatry Res 8:127-136.

Drolet G, Dumont EC, Gosselin I, Kinkead R, Laforest S, Trottier JF (2001) Role of endogenous opioid system in the regulation of the stress response. Prog Neuropsychopharmacol Biol Psychiatry 25:729-741.

Eisenberger NI, Jarcho JM, Lieberman MD, Naliboff BD (2006) An experimental study of shared sensitivity to physical pain and social rejection. Pain 126:132-138.

Eisenberger NI, Lieberman MD, Williams KD (2003) Does rejection hurt? An FMRI study of social exclusion. Science 302:290-292.

Eisenberger NI, Master SL, Inagaki TK, Taylor SE, Shirinyan D, Lieberman MD, Naliboff BD (2011) Attachment figures activate a safety signal-related neural region and reduce pain experience. Proc Natl Acad Sci U S A 108:11721-11726.

Ersek M, Cherrier MM, Overman SS, Irving GA (2004) The cognitive effects of opioids. Pain Manag Nurs 5:75-93.

Friswell J, Phillips C, Holding J, Morgan CJ, Brandner B, Curran HV (2008) Acute effects of opioids on memory functions of healthy men and women. Psychopharmacology (Berl) 198:243-250.

Gentner D, Rattermann MJ, Forbus KD (1993) The roles of similarity in transfer: separating retrievability from inferential soundness. Cogn Psychol 25:524-575.

Gianotti LR, Mohr C, Pizzagalli D, Lehmann D, Brugger P (2001) Associative processing and paranormal belief. Psychiatry and Clinical Neurosciences 55:595-603.

Gospic K, Gunnarsson T, Fransson P, Ingvar M, Lindefors N, Petrovic P (2008) Emotional perception modulated by an opioid and a cholecystokinin agonist. Psychopharmacology (Berl) 197:295-307.

Grevert P, Albert LH, Inturrisi CE, Goldstein A (1983) Effects of eight-hour naloxone infusions on human subjects. Biol Psychiatry 18:1375-1392.

Herman BH, Panksepp J (1978) Effects of morphine and naloxone on separation distress and approach attachment: evidence for opiate mediation of social affect. Pharmacology, biochemistry, and behavior 9:213-220.

Kamboj SK, Tookman A, Jones L, Curran HV (2005) The effects of immediate-release morphine on cognitive functioning in patients receiving chronic opioid therapy in palliative care. Pain 117:388-395.

Koepp MJ, Hammers A, Lawrence AD, Asselin MC, Grasby PM, Bench CJ (2009) Evidence for endogenous opioid release in the amygdala during positive emotion. Neuroimage 44:252-256.

Kut E, Candia V, von Overbeck J, Pok J, Fink D, Folkers G (2011) Pleasure-related analgesia activates opioid-insensitive circuits. J Neurosci 31:4148-4153.

Leknes S, Tracey I (2008) A common neurobiology for pain and pleasure. Nat Rev Neurosci 9:314-320.

Lewis ME, Mishkin M, Bragin E, Brown RM, Pert CB, Pert A (1981) Opiate receptor gradients in monkey cerebral cortex: correspondence with sensory processing hierarchies. Science 211:1166-1169.

Macdonald G, Leary MR (2005) Why does social exclusion hurt? The relationship between social and physical pain. Psychol Bull 131:202-223.

Martin del Campo AF, Dowson JH, Herbert J, Paykel ES (1994) Effects of naloxone on diurnal rhythms in mood and endocrine function: a dose-response study in man. Psychopharmacology (Berl) 114:583-590.

Martin del Campo AF, McMurray RG, Besser GM, Grossman A (1992) Effect of 12-hour infusion of naloxone on mood and cognition in normal male volunteers. Biol Psychiatry 32:344-353.

Mendelson JH, Ellingboe J, Keuhnle JC, Mello NK (1978) Effects of naltrexone on mood and neuroendocrine function in normal adult males. Psychoneuroendocrinology 3:231-236.

Mitchell JP, Macrae CN, Banaji MR (2006) Dissociable medial prefrontal contributions to judgments of similar and dissimilar others. Neuron 50:655-663.

Moles A, Kieffer BL, D'Amato FR (2004) Deficit in attachment behavior in mice lacking the mu-opioid receptor gene. Science 304:1983-1986.

Novick LR (1988) Analogical transfer, problem similarity, and expertise. J Exp Psychol Learn Mem Cogn 14:510-520.

Panksepp J (1998) The Foundations of Human and Animal Emotions. New York: Oxford University Press.

Panksepp J (2003) Neuroscience. Feeling the pain of social loss. Science 302:237-239.

Panksepp J, Herman BH, Vilberg T, Bishop P, DeEskinazi FG (1980) Endogenous opioids and social behavior. Neuroscience and biobehavioral reviews 4:473-487.

Pecina S (2008) Opioid reward 'liking' and 'wanting' in the nucleus accumbens. Physiology & behavior 94:675-680.

Petrovic P, Kalso E, Petersson KM, Ingvar M (2002) Placebo and opioid analgesia-- imaging a shared neuronal network. Science 295:1737-1740.

Pettigrew TF (1958) The measurement and correlates of category width as a cognitive variable. J Pers 26:534-544.

Quirion R, Pilapil C (1991) Distribution of multiple opioid receptors in the human brain. In: Receptors in the Human Nervous System(Mendelsohn, F. A. O. and Paxinos, G., eds) San Diego: Academic Press.

Schaffer CB, Nordahl TE, Schaffer LC, Howe J (2007) Mood-elevating effects of opioid analgesics in patients with bipolar disorder. J Neuropsychiatry Clin Neurosci 19:449-452.

Smith KS, Berridge KC (2007) Opioid limbic circuit for reward: interaction between hedonic hotspots of nucleus accumbens and ventral pallidum. J Neurosci 27:1594-1605.

Stein DJ, van Honk J, Ipser J, Solms M, Panksepp J (2007) Opioids: from physical pain to the pain of social isolation. CNS Spectr 12:669-670, 672-664.

Steyer R, Schwenkmezger P, Notz P, Eid M (1997) MDBF - Mehrdimensionaler Befindlichkeitsfragebogen [Multidimensional Mood questionnaire]. Goettingen, Germany: Hogrefe Verlag

Tourangeau R, Rips LJ, Rasinki K (2000) The Psychology of Survey Response. Cambridge: Cambridge University Press.

Wertheimer M (1923/1958) Principles of perceptual organization. In: Readings in perception(Beardslee, D. C. and Wertheimer, M., eds), pp 115-135 Princeton, NJ: Van Nostrand.

Wise SP, Herkenham M (1982) Opiate receptor distribution in the cerebral cortex of the Rhesus monkey. Science 218:387-389.

Yue X, Vessel EA, Biederman I (2007) The neural basis of scene preferences. Neuroreport 18:525-529.

Zubieta JK, Ketter TA, Bueller JA, Xu Y, Kilbourn MR, Young EA, Koeppe RA (2003) Regulation of human affective responses by anterior cingulate and limbic mu-opioid neurotransmission. Archives of general psychiatry 60:1145-1153.

Figure Legends

Figure 1: Time course of the stimulations for the similarity judgment run (SJ) (**A**) and the dissimilarity judgment run (DJ) (**B**). After 750 ms (fixation of a central cross), a stimulus consisting of two horizontally placed meaningless geometric objects was bilaterally exposed for 150 ms (balanced for object side order). Subsequently, the degree of similarity or dissimilarity by clicking on the computerized VAS had to be indicated. In order to control the baseline mouse position, participants had to click on the fixation cross in the middle of the screen after each judgment (which elicited the next trial). Participants were instructed to respond as quickly and as intuitively as possible and to fixate their gaze on a cross in the center of the screen.

Figure 2: VAS magnitude score (in percent) for the two substance groups (naloxone, placebo) and the two runs (SJR, DJR) (mean ± standard error). Because all participants

indicated mean VAS scores above 50%, the illustrated scale range has been adapted to be read from 50 to 75%. Asterisks (*) indicate significant post-hoc comparisons (*P < 0.05).

Figure 3: Ambigram “Identical / Opposite” created by the American graphic designer Scott Kim in 1989. © Scott Kim, scottkim.com.